**EXHIBIT D: CLEAN VERSION OF PENDING CLAIMS**
U.S. APPLICATION SERIAL NO. To be assigned
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(as amended April 2, 2001)

1. (Amended) A method for evaluating specificity of a drug comprising comparing activity of said drug against its target pathway ($D_{target}$) in a biological sample and activity of said drug against at least one off-target pathway ($D_{off\text{-}target}$) in said biological sample, wherein said $D_{target}$ and $D_{off\text{-}target}$ are based on measurements of a plurality of cellular constituents.

2. The method of Claim 1 wherein said $D_{target}$ and $D_{off\text{-}target}$ are measured according to a method comprising:

a) applying a plurality of levels of said drug to said biological sample and measuring a plurality of cellular constituents in said biological sample at each level of said drug to obtain a first profile of graded drug response;

b) applying said plurality of levels of said drug to a test sample, wherein said test sample is the same as said biological sample except that said target pathway is not functional, and measuring said plurality of cellular constituents in said test sample at each level of said drug to obtain a second profile of graded drug response; and

c) determining said $D_{target}$ and $D_{off\text{-}target}$ by comparing said first and second profiles.

3. The method of claim 2 wherein said biological sample is a yeast cell and said test sample is a yeast cell with a critical gene in said target pathway being deleted.

4. The method of claim 2 wherein said biological sample is a mammalian cell and said test sample is a mammalian cell with a critical gene in said target pathway being deleted.

5. The method of claim 2 wherein said biological sample is an animal and said test sample is a transgenic animal with a critical gene in said target pathway being made nonfunctional.

6. The method of claim 2 wherein said plurality of cellular constituents are transcripts of a plurality of genes.

7. The method of claim 2 wherein said plurality of cellular constituents are proteins.

8. The method of claim 1 wherein said $D_{target}$ and $D_{off\text{-}target}$ are measured according to a method comprising:

a) perturbing said target pathway and/or said off target pathway in said biological sample to obtain a perturbation profile consisting of a plurality of cellular constituent measurements;

b) applying a plurality of levels of said drug to said biological sample to obtain a drug response profile consisting of a plurality of cellular constituent measurements at each level of said drug; and

c) decomposing said $D_{target}$ and $D_{off\text{-}target}$ by comparing said drug response profile and said perturbation profile.

9. The method of claim 8 wherein said plurality of cellular constituents are transcripts of a plurality of genes.

10. The method of claim 8 wherein said plurality of cellular constituents are proteins.

11. The method of claim 1 wherein said determining step comprises calculating a specificity index (SI) according to the following formulae:

$$SI = \frac{n \bullet D_{target}}{\sum D_{off-target}}$$

wherein: n is the number of said off-target pathways.

12. (Amended) A method for evaluating specificity of a drug comprising:

a) measuring activity of said drug against its target pathway to obtain a target activity ($D_{target}$);

b) measuring activity of said drug against at least one pathway other than said target pathway to obtain at least one off-target activity ($D_{off\text{-}target}$); and

c) determining said specificity by comparing said target activity and said off-target activity;

wherein said $D_{target}$ and $D_{off\text{-}target}$ are based on measurements of a plurality of cellular constituents.

13. The method of claim 12 wherein said $D_{target}$ and $D_{off\text{-}target}$ are measured according to a method comprising:

a) applying a plurality of levels of said drug to said biological sample and measuring a plurality of cellular constituents in said biological sample at each level of said drug to obtain a first profile of graded drug response;

b) applying said plurality of levels of said drug to a test sample, wherein said test sample is the same as said biological sample except that said target pathway is not functional, and measuring said plurality of cellular constituents in said test sample at each level of said drug to obtain a second profile of graded drug response; and

c) determining said $D_{target}$ and $D_{off\text{-}target}$ by comparing said first and second profiles.

14. The method of claim 13 wherein said plurality of cellular constituents are transcripts of a plurality of genes.

15. The method of claim 13 wherein said plurality of cellular constituents are proteins.

16. The method of claim 13 wherein said biological sample is a yeast cell and said test sample is a yeast cell with a critical gene in said target pathway being deleted.

17. The method of claim 13 wherein said biological sample is a mammalian cell and said test sample is a mammalian cell with a critical gene in said target pathway being deleted.

18. The method of claim 13 wherein said biological sample is an animal and said test sample is a transgenic animal with a critical gene in said target pathway being made nonfunctional.

19. The method of claim 12 wherein said $D_{target}$ and $D_{off\text{-}target}$ are measured according to a method comprising:

a) perturbing said target pathway and/or said off target pathway in said biological sample to obtain a perturbation profile consisting of a plurality of cellular constituent measurements;

b) applying a plurality of levels of said drug to said biological sample to obtain a drug response profile consisting of a plurality of cellular constituent measurements at each level of said drug; and

c) decomposing said $D_{target}$ and $D_{off\text{-}target}$ by comparing said drug response profile and said perturbation profile.

20. The method of claim 19 wherein said plurality of cellular constituents are transcripts of a plurality of genes.

21. The method of claim 20 wherein said plurality of cellular constituents are proteins.

22. The method of claim 12 wherein said determining step comprises calculating a specificity index (SI) according to the following formulae:

$$SI = \frac{n \bullet D_{target}}{\sum D_{off-target}}$$

wherein: n is the number of said off-target pathways.

23. (Amended) A method of determining therapeutic index of a drug in a biological sample comprising:

determining said therapeutic index according to the formula: $TI = C_{target} / C_{off\text{-}target}$, wherein $C_{target}$ is a minimum effective concentration needed to induce a threshold response in a target pathway and $C_{off\text{-}target}$ is the minimum toxic concentration needed to induce a threshold response in at least one off-target pathway.

24. (Amended) The method of claim 23 wherein said $C_{target}$ and $C_{off\text{-}target}$ are measured according to a method comprising:

a) applying a plurality of levels of said drug to said biological sample and measuring a plurality of cellular constituents at each level of said drug in said biological sample to obtain a first profile of graded drug response;

b) applying said plurality of levels of said drug to a test sample, wherein said test sample is the same as said biological sample except that said target pathway is not functional, and measuring a plurality of cellular constituents in said test sample at each level of said drug, to obtain a second profile of graded drug response; and

c) determining said $C_{target}$ and $C_{off\text{-}target}$ by comparing said first and second profiles.

25. The method of claim 24 wherein said plurality of cellular constituents are transcripts of a plurality of genes.

26. The method of claim 24 wherein said plurality of cellular constituents are proteins.

27. The method of claim 24 wherein said biological sample is a yeast cell and said test sample is a yeast cell with a critical gene in said target pathway being deleted.

28. The method of claim 24 wherein said biological sample is a mammalian cell and said test sample is a mammalian cell with a critical gene in said target pathway being deleted.

29. The method of claim 24 wherein said biological sample is an animal and said test sample is a transgenic animal with a critical gene in said target pathway being made nonfunctional.

30. The method of claim 24 wherein said target threshold response is at least two fold induction or repression of a plurality of cellular constituents in said target pathway.

31. The method of claim 24 wherein said off-target threshold response is at least two fold induction or repression of a plurality of cellular constituents in said off-target pathway.

32. The method of claim 23 wherein said target threshold response is a response that is sufficient to have a therapeutic effect.

33. The method of claim 23 wherein said off-target threshold response is a response that is sufficient to constitute a toxic effect.

34. (Amended) A method of determining a therapeutic index of a drug in a biological sample comprising:

a) applying a plurality of levels of said drug to said biological sample;

b) determining a minimum effective concentration ($C_{target}$) needed to induce a threshold response in a target pathway, wherein said drug exerts its pharmacological activity through said target pathway;

c) determining a minimum toxic concentration ($C_{off\text{-}target}$) needed to induce a threshold response in at least one off-target pathway; and

d) determining said therapeutic index according to the formula: $TI = C_{target} / C_{off\text{-}target}$.

35. The method of claim 34 wherein said $C_{target}$ and $C_{off\text{-}target}$ are measured according to a method comprising:

a) applying a plurality of levels of said drug to said biological sample and measuring a plurality of cellular constituents at each level of said drug in said biological sample to obtain a first profile of graded drug response;

b) applying said plurality of levels of said drug to a test sample, wherein said test sample is the same as said biological sample except that said target pathway is not functional, and measuring a plurality of cellular constituents in said test sample at each level of said drug to obtain a second profile of graded drug response; and

c) determining said $C_{target}$ and $C_{off\text{-}target}$ by comparing said first and second profiles.

36. (Amended) The method of claim 35 wherein said plurality of cellular constituents are transcripts of a plurality of genes.

37. The method of claim 35 wherein said plurality of cellular constituents are proteins.

38. The method of claim 35 wherein said biological sample is a yeast cell and said test sample is a yeast cell with a critical gene in said target pathway being deleted.

39. The method of claim 36 wherein said biological sample is a mammalian cell and said test sample is a mammalian cell with a critical gene in said target pathway being deleted.

40. The method of claim 36 wherein said biological sample is an animal and said test sample is a transgenic animal with a critical gene in said target pathway being made nonfunctional.

41. The method of claim 35 wherein said target threshold response is at least two fold induction or repression of a plurality of cellular constituents in said target pathway.

42. The method of claim 35 wherein said off-target threshold response is at least two fold induction or repression of a plurality of cellular constituents in said off-target pathway.

43. The method of claim 35 wherein said target threshold response is a response that is sufficient to have a therapeutic effect.

44. The method of claim 35 wherein said off-target threshold response is a response that is sufficient to constitute a toxic effect.

64. (New) A method for evaluating specificity of a drug, said method comprising:

(a) decomposing a drug response profile into one or a combination of pathway response profiles, wherein said drug response profile comprises measurements of a plurality of cellular constituents in a biological sample in response to said drug over a plurality of levels of drug exposure, and each said pathway response profile comprises measurements of a plurality of cellular constituents at a plurality of levels of perturbation to a biological pathway; and

(b) comparing, among said one or a combination of pathway response profiles, the pathway response profiles for the one or more biological pathways associated with therapeutic effects of the drug with the pathway response profiles for the one or more

biological pathways that are associated with one or more non-therapeutic effects of the drug, thereby comparing activity of said drug on its target pathway ($D_{target}$) and at least one off-target pathway ($D_{off\text{-}target}$) and evaluating specificity of said drug.

65. (New) The method of claim 64, further comprising transforming said levels of drug exposure into said levels of perturbation by a horizontal scaling transformation.

66. (New) The method of claim 65, wherein said horizontal scaling transformation is a linear transformation.

67. (New) The method of claim 65, wherein said decomposing comprises determining said scaling transformation such that said drug response profile is represented by said one or a combination of pathway response profiles.

68. (New) The method of claim 67, wherein said determining is by a method comprising least squares minimizing the residue between said drug response profile and said one or a combination of pathway response profiles.

69. (New) The method of claim 64, wherein values of said measurements of a plurality of cellular constituents have been converted into cellular constituent set values.

70. (New) A method for evaluating specificity of a drug, said method comprising decomposing a drug response profile into one or a combination of pathway response profiles, wherein said drug response profile comprises measurements of a plurality of cellular constituents in a biological sample in response to said drug over a plurality of levels of drug dosage, and each said pathway response profile comprises measurements of a plurality of cellular constituents at a plurality of levels of perturbation to a biological pathway, thereby evaluating specificity of said drug.